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## WO9919300A1: PROSTAGLANDIN AGONISTS AND THEIR USE TO TREAT BONE DISORDERS

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**Inventor(s):** CAMERON, Kimberly, O'Keefe , 5 North Winchester Court, East Lyme, CT 06333, United States of America  
LEFKER, Bruce, Allen , 21 Eagle Ridge Drive, Gales Ferry, CT 06355, United States of America  
ROSATI, Robert, Louis , 71 Deans Mill Road, Stonington, CT 06378, United States of America

**Applicant(s):** PFIZER INC., 235 East 42nd Street, New York, NY 10017, United States of America

**Issued/Filed Dates:** April 22, 1999 / Oct. 5, 1998

**Application Number:** WO1998IB0001540

**IPC Class:** C07D 213/71; C07C 311/13; C07D 401/12; C07D 405/12; C07D 409/12; C07D 417/12; C07D 233/84; C07D 403/12; A61K 031/18; A61K 031/40; A61K 031/415; A61K 031/435; A61K 031/425; A61K 031/505;

**Designated Countries:** AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, European patent: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, OAPI patent: BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG, ARIPO patent: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, Eurasian patent: AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

**Abstract:**

This invention relates to prostaglandin agonists, methods of using such prostaglandin agonists, pharmaceutical compositions containing such prostaglandin agonists and kits containing such prostaglandin agonists. The prostaglandin agonists are useful for the treatment of bone disorders including osteoporosis.

[\[Show "fr" Abstract\]](#)

**Attorney, Agent, or Firm:**  
SPIEGEL, Allen, J.;

**Foreign References:** none

(No patents reference this one)

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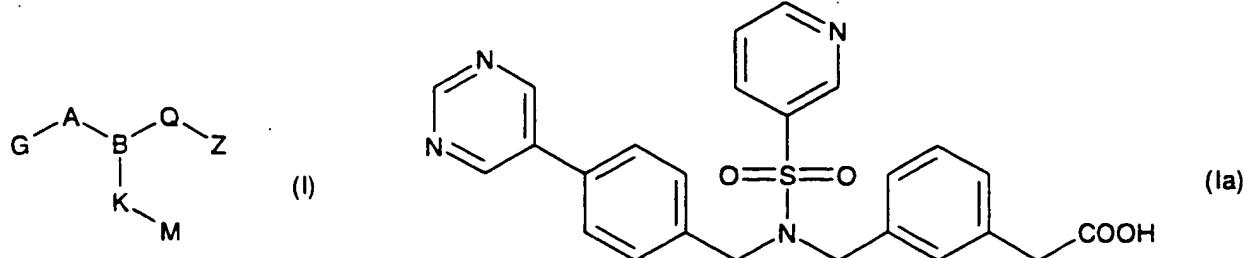
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**New prostaglandin agonists - useful for the treatment of bone diseases (e.g. osteoporosis), kidney degeneration and glaucoma.**

**Drug Activity:** Osteopathic; Antiinflammatory; Nephrotropic; Ophthalmological; Hypotensive

**Mechanism of Action:** Prostaglandin-Agonist

**Compound Name:** None Given



**Use:** For the treatment of osteoporosis (e.g. glucocorticoid-induced osteoporosis), osteotomy, childhood idiopathic bone loss or bone loss associated with periodontitis; for augmenting and maintaining bone mass (e.g. following facial reconstruction or treating bone fracture); for treating kidney degeneration, glaucoma, ocular hypertension (claimed) and as prostaglandin agonists.

**Dosage:** 0.001-100 (0.01-10) mg/kg/day. Administration may be systemic or local, such as oral, parenteral and intraduodenal.

**Advantage:** None given.

**Biological Data:** No data given.

**Chemistry:** Compounds of formula (I) and their prodrugs and salts are new.

A =  $\text{SO}_2$  or CO; G = a defined aryl or bi-aryl containing group, arylamino, or R<sub>1</sub>R<sub>2</sub>-amino.

R<sub>1</sub>,R<sub>2</sub> = H or alkyl, or together NR<sub>1</sub>R<sub>2</sub> is a 5/6-membered heterocycle; B = N, or CH; Q = a defined divalent linking group such as alkylene optionally substituted and optionally interrupted by an aromatic ring.

Z = carboxyl, alkoxy carbonyl, tetrazolyl, 1,2,4-oxadiazolyl, 5-oxo-1,2,4-oxadiazolyl, 5-oxo-1,2,4-thiadiazolyl, alkylsulfonylcarbamoyl, or phenylsulfonylcarbamoyl; K = a bond, or alkylene optionally substituted and optionally interrupted by O or S; M = defined aryl, or defined biaryl (in which the aryl groups are linked via a heteroatom, a divalent linking group (e.g. alkylene) or directly by a bond); Provisos are given.

Several compounds are specifically claimed e.g. (3-(((pyridine-3-sulfonyl)-(4-pyrimidin-5-yl-benzyl)-amino)-methyl)-phenyl)-acetic acid (la) (example la).

249 pages

Drawings 0/0

**Authors:** Cameron K O; Lefker B A; Rosati R L

**Location:** New York, N.Y., USA

**Publication Date:** 22 April 1999

**Document Number:** WO9919300-A1

**Language:** English

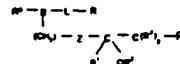
**Filed:** 05 October 1998 as IB1540

**Priority:** 10 October 1997 US-061727

**Designated States:** Regional: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE (ARIPO)  
(Eurasian) (OAPI) National: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW

EP911321

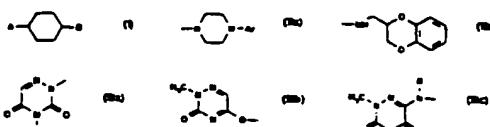
Pfizer

 <b>European Patent Office</b> Office Europeen des brevets	<b>EP 0 911 321 A2</b> <b>EUROPEAN PATENT APPLICATION</b> (11) Date of publication 26.01.1995 Document 090911 (12) Application number 92305191.1 (21) Date of filing 05.10.1992 (22) Designation Concerning States AT BE CH CY DE DK FR GB IE IT LU NL SE SI PT BE Designation European States AL LT LV SK BG RO (23) Priority 10.10.1992 US 51662 P (24) Applicant PFIZER INC New York, NY 10017 (US) (25) Inventor • Common, Randolph O'Leary East Lynn, Massachusetts 01920 (US)	(11) Inv. C 097C 311/13 C07C 317/10 C07C 317/44 C07D 323/40 C07D 307/68 C07D 307/74 C07D 277/56 C07D 213/70 A61K 31/24, A61K 31/30 A61K 314/25, A61K 314/4
		* Lancer Group Inventor James Perry, Cambridge 02133 (US) • Recuit, Robert Louis Somerville, Massachusetts 02145 (US)
		(74) Representative: Hopkins, James Richard & Co 100 London Palace Chambers, Somergate Road Somerton, Avon CT12 3HU (GB)
(54) Compounds for the treatment of osteoporosis		
<small>(57) The invention relates to pharmaceutical compositions containing agonists or antagonists of bone resorption receptors, the pharmaceutical compositions being useful for the treatment of bone diseases including osteoporosis.</small>		
<b>Structure is taken from Page 3 of the specification.</b>		
		

EP0911321 A2

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Pierre Fabre

 <b>PIERRE FABRE MEDICAMENT</b> (FR) 45 avenue André Gide F-62160 Béthune-Bruay (FR) (13) International Patent Classification C07D 209/6, A61K 31/12, C07D 323/12 (14) Inv. Publication Number WO 9920613 (15) Inv. Publication Date 29 April 1999 (16) Inv. Application Number PCT/FR98/02201 (17) International Filing Date 14 October 1998 (18) Inv. Priority Date 14 October 1998 (19) Inv. Language of application English (20) Inv. Language of international publication English (21) Assignee PIERRE FABRE MEDICAMENT (FR) 45 avenue André Gide F-62160 Béthune-Bruay (FR) (22) Inventor(s) and PATOISEAU Jean-Pierre (FR) 7, rue Anne Ferry F-61100 Couëres (FR) DUPONT-PASSELAIGUE, Etienne (FR) 22, rue du Général Sarrail F-61100 Couëres (FR) KERK, Yves (FR) Laboratoire "Les Mésanges" F-61280 Vireux-Molhainne (FR) (23) Application Report HAMITOU, Jean-Paul, Couëres, France F-61110 Paris (FR) (24) Designated States AU BR CA CH JP MA US EP IAT BE CH CY DE DK ES FI FR GB OR IE IT LU MC NL PT BE (25) Inv. CYCLOHEXANE DERIVATIVES & FUNCTIONALISED 1,4-AB LOIANS OF 5-HT <sub>1A</sub> RECEPTORS	(11) Inv. Publication Number WO 9920613 (12) International Publication Date 29 April 1999 (13) Inv. Number 097C 311/13 C07C 317/10 (14) Date 16 October 1997 (15) Inv. Application Number PCT/FR98/02201 (16) Inv. Priority Date 14 October 1998 (17) International Filing Date 14 October 1998 (18) Inv. Language of application English (19) Inv. Language of international publication English (20) Inv. Language of application English (21) Assignee PIERRE FABRE MEDICAMENT (FR) 45 avenue André Gide F-62160 Béthune-Bruay (FR) (22) Inventor(s) and PATOISEAU Jean-Pierre (FR) 7, rue Anne Ferry F-61100 Couëres (FR) DUPONT-PASSELAIGUE, Etienne (FR) 22, rue du Général Sarrail F-61100 Couëres (FR) KERK, Yves (FR) Laboratoire "Les Mésanges" F-61280 Vireux-Molhainne (FR) (23) Application Report HAMITOU, Jean-Paul, Couëres, France F-61110 Paris (FR) (24) Designated States AU BR CA CH JP MA US EP IAT BE CH CY DE DK ES FI FR GB OR IE IT LU MC NL PT BE (25) Inv. CYCLOHEXANE DERIVATIVES & FUNCTIONALISED 1,4-AB LOIANS OF 5-HT <sub>1A</sub> RECEPTORS
	

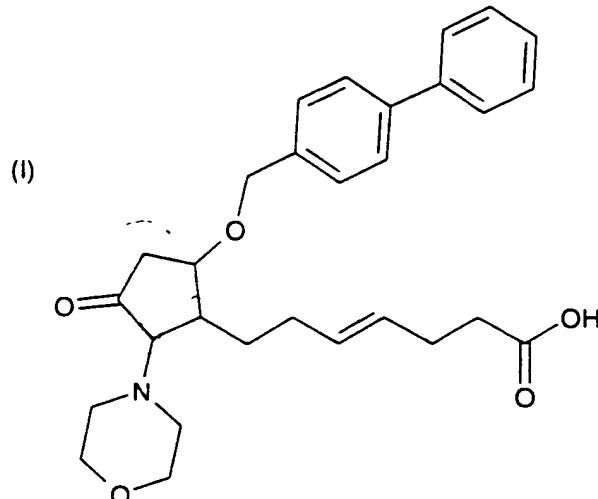
1-4 Difunctionalised cyclohexane and 3-oxo-2(H)-1,2,4-triazine derivatives as 5-HT<sub>1A</sub> receptor ligands. Related to compounds claimed by Patoiseau and Dupont-Passelaigue in WO9501965 and WO9616949.

**Use of EP4 receptor antagonists as bone resorption inhibitors - for the treatment of osteoarthritis, rheumatoid arthritis, osteoporosis, inflammatory bone diseases and hypocalcemia.**

**Drug Activity:** Osteopathic; Antiarthritic; Antirheumatic; Antiinflammatory; Cardiovascular-Gen.

**Mechanism of Action:** Prostaglandin-Antagonist-EP4; Prostaglandin-Antagonist-E2

**Compound Name:** None Given



**Use:** As EP4 antagonists for the treatment of conditions with accelerated bone resorption (claimed) e.g. osteoarthritis, rheumatoid arthritis, osteoporosis, inflammatory bone diseases and hypocalcemia.

**Dosage:** 0.1-200 (0.1-10) mg/kg/day. Administration may be oral, parenteral, rectal or by inhalation.

**Advantage:** The compounds prevent accelerated bone resorption by inhibiting PGE<sub>2</sub>-stimulated osteoclast-like cell formation in bone marrow.

**Biological Data:** None given.

**Chemistry:** The use of an EP4 antagonist in the treatment of conditions with accelerated bone resorption is claimed.

Preferably the EP4 antagonist is [ $1\alpha(Z),2\beta,5\alpha$ ]-( $\pm$ )-7-[5-[(1,1'-biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)-3-oxocyclopentyl]-4-heptenoic acid (I) or its [ $1R|1\alpha(Z),2\beta,5\alpha$ ]-( $-$ )-isomer or their salts and solvates.

7 pages

Drawings 0/0

**Authors:** Foord S M; Sheldrick R L G; Lumley P

**Location:** Greenford, U.K.

**Publication Date:** 21 April 1999

**Document Number:** GB2330307-A

**Language:** English

**Filed:** 07 February 1998 as 002599

**Priority:** 07 February 1998 GB-002599

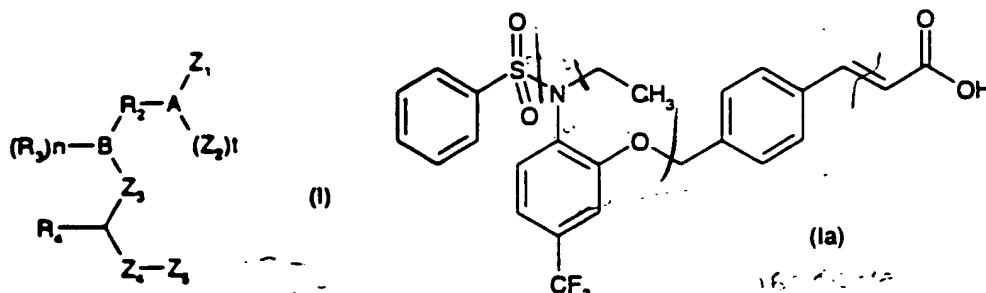
*112*

New sulfonamide and carboxamide derivatives bind to prostaglandin E2 receptors - useful for e.g. promoting and inhibiting digestive tract motility, causing analgesia and as hypotensives.

**Drug Activity:** Inotropic-Pos.; Inotropic-Neg.; Gynecological; Gastrointestinal-Gen.; Analgesic; Sedative; Vasotropics; Hypotensive; Diuretic; Antidiarrheic; Antidiabetic; Antiulcer; Antiinflammatory; Tocolytic; Laxative; Tranquilizer

**Mechanism of Action:** Prostaglandin-Agonist-E2; Prostaglandin-Antagonist-E2

**Compound Name:** None Given



**Use:** As antagonists and agonists of prostaglandin E2 (PGE2) receptors for promoting or inhibiting uterine muscle contraction or digestive tract movement, as analgesics or hypnotics, for enlarging vascular capacity, for suppressing gastric acid secretion, and as hypotensives or diuretics, for treating diarrhea, diabetes, gastric ulcers, gastritis, to aid sleep and as antabortionfacient, laxatives and tranquilizers.

**Dosage:** 1 µg-100 mg/day orally or 0.1 µg-10 mg/day parenterally.

**Advantage:** None given.

**Biological Data:** In a PGE2 receptor binding assay (la) had a Ki of 0.0002 µM.

**Chemistry:** Sulfonamide and carboxamide derivatives of formula (I) and their salts are new. ring A, ring B = 5-15C carbocyclyl or 5-7 membered heterocyclyl containing 1 or 2 O, N or S; Z1 = COR1, 1-4C alkylene-COR1, CH=CHCOR1, C=CCOR1, O-1-3C alkylene-COR1, or 1-5C alkylene-OH; R1 = OH 1-4C alkoxy or optionally substituted NH2; Z2 = H, 1-4C alkyl, 1-4C alkoxy, NO2, halo, CF3, CF3O, OH or COR1; Z3 = bond or 1-4C alkylene; Z4 = SO2 or CO; Z5 = 1-8C alkyl, 2-8C alkenyl, 2-8C alkynyl, optionally substituted cycloalkyl, phenyl or heterocyclyl or substituted alkyl, alkenyl or alkynyl; R2 = O, S, CO, or optionally substituted imino, CONH, NHCO or alkylene; R3 = H, 1-6C alkyl, 1-6C alkoxy, 1-6C alkylthio, NO2, halo, CF3, CF3O, OH or CH2OH; R4 = H, 2-8C alkenyl, 2-8C alkynyl or optionally substituted alkyl; n, i = 1-4; provided that when A = a benzene ring and (Z2)i = COR1 then Z1 is bonded to the 3 or 4 position of A.

(I) is e.g. 4-[2-(N-ethylphenylsulphonylamino)-5-trifluoromethylphenoxy]methyl cinnamic acid (la).

305 pages

Drawings 0/0

Authors: Otuchida S; Nagao Y

Location: Osaka, Japan

Publication Date: 25 June 1998

Document Number: WO9827053-A1

Language: Japanese

Filed: 12 December 1997 as J04593

Priority: 21 October 1997 JP-305055

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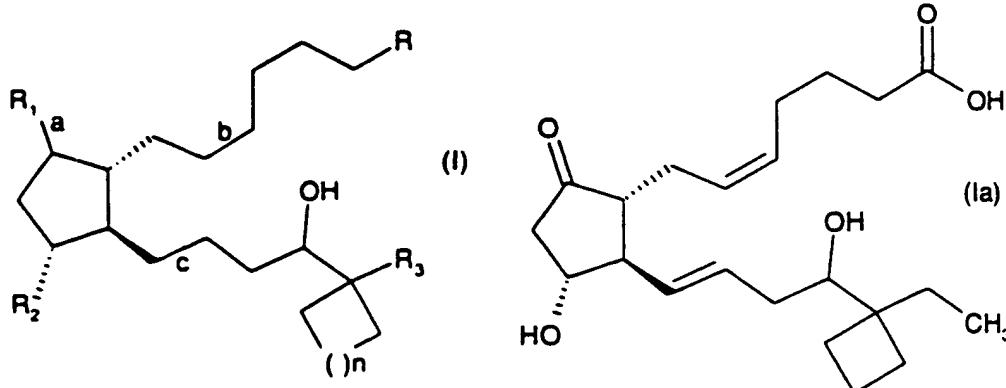
CN HU JP KR MX NO US

WD-98-008828

TX / 1431

New  $\omega$ -cycloalkylprostaglandin E2 derivatives are EP2 receptor modulators - useful for the treatment of e.g. immunological diseases, asthma and abnormal bone formation.

**Drug Activity:** Immunomodulator; Antiasthmatic; Osteopathic; Neuroprotective; Hepatotropic; Antiinfertility; Tocolytic; Ophthalmological  
**Mechanism of Action:** Prostaglandin-Antagonist-EP2; Prostaglandin-Agonist-EP2  
**Compound Name:** None Given



**Use:** As EP2 receptor modulators and for the treatment and prevention of immunological diseases, asthma, abnormal bone formation, neuronal cell death, liver damage, abortion, premature birth or retina neuropathy of glaucoma (claimed).

**Dosage:** 1  $\mu$ g-100 mg orally; 0.1  $\mu$ g-10 mg parenterally. Administration is also rectal.

**Advantage:** Improved specificity and reduced side effects.

**Biological Data:** Compounds of the invention were assayed for activity against prostanoide receptor subtypes. Compound (la) showed K<sub>i</sub> values of > 10, 0.030, > 10 and > 10  $\mu$ M for receptors EP1, EP2, EP3 $\alpha$  and EP4 respectively.

**Chemistry:**  $\omega$ -Cycloalkyl-prostaglandin E2 derivatives of formula (I) and their salts and cyclodextrin clathrates are new.

R = COOH or CH<sub>2</sub>OH; R<sub>1</sub> = oxo, CH<sub>2</sub> or halo; R<sub>3</sub> = alkyl, alkenyl, alkynyl (all optionally substituted) or H; n = 0-4; a = optional double bond; b = optional double or triple bond; c = optional single, double or triple bond; Provisos are given.

Several compounds are specifically claimed e.g. (5Z,11 $\alpha$ 13E)-11,16-dihydroxy-9-oxo-17,17-propeno-20-norprosta-5,13-dienoic acid (la) (example 4(10)).

121 pages

Drawings 0/0

**Authors:** Tani K; Ohuchida S

**Publication Date:** 26 August 1998

**Language:** English

**Priority:** 06 November 1997 JP-319169

**Location:** Osaka, Japan

**Document Number:** EP-860430-A2

**Filed:** 03 February 1998 as 300769

**Designated States:** AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE

WD-98-010805

PP - Gastrointestinal, Inflammation & Allergy

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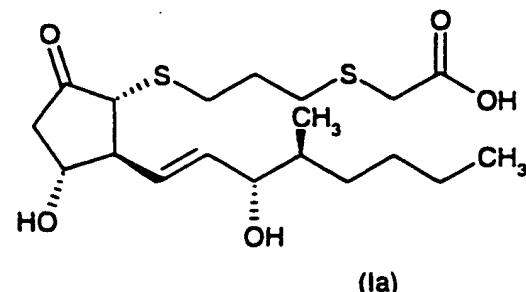
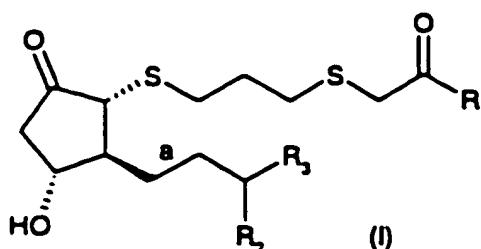
New 3,7-di thiaprostanic acid derivatives - useful for the treatment and prevention of e.g. immunological disease, asthma, abnormal bone formation and neuronal cell death.

**Drug Activity:** Immunosuppressive; Immunostimulant; Antiasthmatic; Osteopathic; Neuroprotective;

Hepatotropic; Nephrotropic; Antiinflammatory; Hypotensive; Cardiant; Vasotropic

**Mechanism of Action:** Prostaglandin-Agonist-E2; Prostaglandin-Agonist-EP4

**Compound Name:** None Given



**Use:** For the treatment and prevention of immunological diseases e.g. autoimmune diseases, immunological deficiency diseases and organ transplantation, asthma, abnormal bone formation, neuronal cell death, liver damage, nephritis, hypertension and myocardial ischemia (claimed).

**Dosage:** 1 µg-100 mg orally up to several times per day; 0.1 µg-10 mg parenterally up to several times per day. Administration may also be topical, rectal or vaginal.

**Advantage:** None given.

**Biological Data:** Membrane fraction was prepared using the prostanoid receptor subtypes (mouse EP3 $\alpha$ , EP4) expressing CHO cells. A standard assay mixture containing membrane fraction (0.5 mg/ml), 2.5 nM of  $^3$ H-PGE<sub>2</sub> and various concentrations of the test compounds was incubated for 1 hour at room temperature. The reaction was terminated by the addition of ice-cold buffer. K<sub>d</sub> and B<sub>max</sub> values were determined and non-specific binding was calculated as the bound in the presence of an excess of unlabeled PGE<sub>2</sub>. The dissociation constant (K<sub>i</sub>) was then determined, and (Ia) produced a K<sub>i</sub> of 0.0002  $\mu$ M for EP4 receptor subtypes.

**Chemistry:** 3,7-Dithiaprostanic acid derivatives of formula (I) and their salts and cyclodextrin clathrates are new.

R1 = OH, 1-4C alkoxy or NR6R7; R6, R7 = independently H or 1-4C alkyl; R2 = H or OH; R3 = optionally substituted 1-8C alkyl, optionally substituted 2-8C alkenyl, optionally substituted 2-8C alkynyl, Ph or 3-7C cycloalkyl; a = double or single bond; the derivative may include the 8-epi equilibrium compound; provisos are given.

Several compounds are specifically claimed e.g. 11 $\alpha$ ,15 $\alpha$ -dihydroxy-9-oxo-16 $\beta$ -methyl-3,7-dithiaprost-13E-enoic acid (Ia) (Example 2(o)).

39 pages

Drawings 0/0

**Authors:** Maruyama T; Ohuchida S

**Location:** Osaka, Japan

**Publication Date:** 29 July 1998

**Document Number:** EP-855389-A2

**Language:** English

**Filed:** 26 January 1998 as 300513

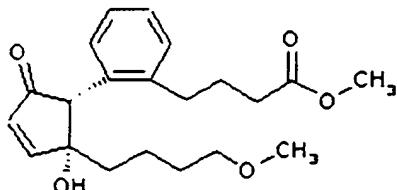
**Priority:** 27 January 1997 JP-027198

**Designated States:** AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE

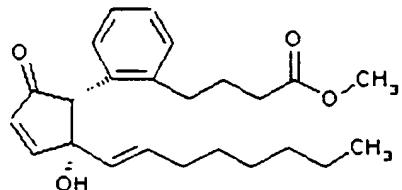
WD-98-009700

[Front Page](#)**[April 16, 1999] New series of osteogenesis-promoting agents developed at Taisho**

Taisho scientists have prepared and evaluated two series of **phenyl-substituted hydroxycyclopentenone analogues with osteogenesis-promoting effects**. Compounds of the invention were found to significantly increase Ca<sup>2+</sup> and alkaline phosphatase (ALP) in human long bone osteoblast cultures at a concentration of 5 nM (JP 99043460 and JP 99043459).



JP 99043460



JP 99043459

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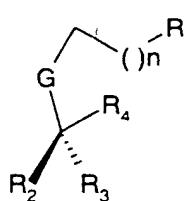
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**Use of tetrahydrofuran prostaglandin analogs as prostaglandin DP/FP receptor agonists - for the treatment of glaucoma and ocular hypertension.**

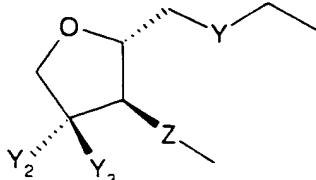
**Drug Activity:** Ophthalmological; Hypotensive

**Mechanism of Action:** Prostaglandin-Agonist

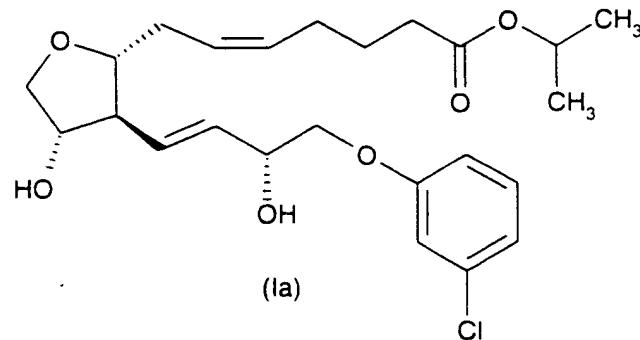
**Compound Name:** None Given



(I)



(i)



(Ia)

**Use:** For treating glaucoma and ocular hypertension (claimed). As agonists at the prostaglandin DP and FP receptors.

**Dosage:** 0.00003-0.5 (0.001-0.01) wt% solution for topical administration to the eye.

**Advantage:** Improved therapeutic profile compared to natural prostaglandins.

**Biological Data:** No data given.

**Chemistry:** The use of prostaglandin analogs of formula (I) for treating glaucoma or ocular hypertension is claimed.

R = an ester, CO<sub>2</sub>R<sub>1</sub>, CONR<sub>7</sub>R<sub>8</sub>, CH<sub>2</sub>OR<sub>9</sub> or CH<sub>2</sub>NR<sub>10</sub>R<sub>11</sub>; R<sub>1</sub> = H, or a cationic salt or ammonium moiety; R<sub>7</sub>,R<sub>8</sub> = independently H or alkyl; R<sub>9</sub> = H, acyl, or alkyl; R<sub>10</sub>,R<sub>11</sub> = independently H, acyl or alkyl (providing only one is acyl); n = 0 or 2; G = a group of formula (i) or two other defined tetrahydrofuran containing moieties; Y = CH<sub>2</sub>CH=CH (cis), CH=CHCH<sub>2</sub> (cis) or CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>; Z = CC, CH=CH (trans) or CH<sub>2</sub>CH<sub>2</sub>; one of Y<sub>2</sub>,Y<sub>3</sub> = H, and the other = F or OH (which may be modified); R<sub>4</sub> = cyclohexyl, 5-7C alkyl or R<sub>5</sub>; R<sub>5</sub> = (CH<sub>2</sub>)<sub>m</sub>Xphenyl or (CH<sub>2</sub>)<sub>p</sub>Z<sub>2</sub>; X = O or CH<sub>2</sub>; m = 1-6; phenyl is optionally substituted with halo, CH<sub>3</sub>, CF<sub>3</sub>, CN, OCH<sub>3</sub> or acetyl; p = 0-6; Z<sub>2</sub> = a defined optionally substituted bicyclic carbocycle or O-containing heterocycle; Several provisos are given.

(I) is e.g. isopropyl [2R(5Z),3S(1E,3R),4S]-7-[tetrahydro-3-[4-(3-chlorophenoxy)-3-hydroxy-1-butenyl]-4-hydroxy-2-furanyl]-5-heptenoate (Ia) (compound VI).

24 pages

Drawings 0/0

**Authors:** Selliah R D

**Publication Date:** 23 December 1998

**Language:** English

**Priority:** 18 June 1997 US-878030

**Location:** Fort Worth, Tex., USA

**Document Number:** WO9857942-A1

**Filed:** 03 June 1998 as U11339

**Designated States:** Regional: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE National: AU BR CA JP MX US

WD-99-000792

PP - Cardiovascular

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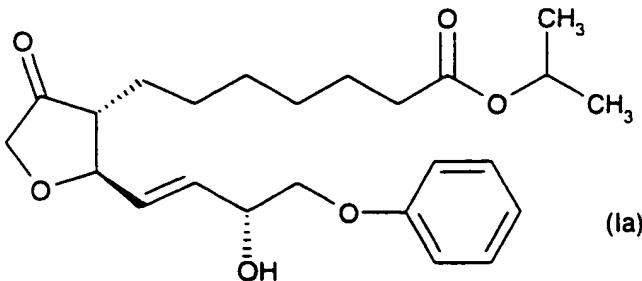
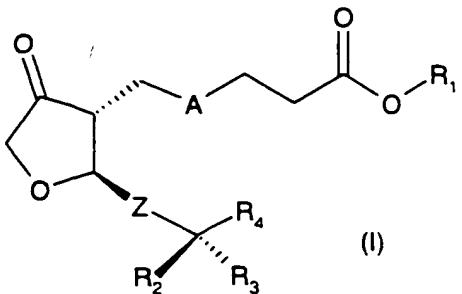
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**Use of tetrahydrofuran prostanoid analogs as prostaglandin receptor agonists - for the treatment of glaucoma and ocular hypertension.**

**Drug Activity:** Ophthalmological; Hypotensive

**Mechanism of Action:** Prostaglandin-Agonist

**Compound Name:** None Given



**Use:** For treating glaucoma or ocular hypertension (claimed). As agonists at the prostaglandin EP receptor.

**Dosage:** 0.00003-0.5 (0.001-0.01) wt% solution for topical administration to the eye.

**Advantage:** Improved therapeutic profile compared to natural prostaglandins.

**Biological Data:** No suitable data given.

**Chemistry:** The use of prostaglandin analogs of formula (I) for treating glaucoma or ocular hypertension is claimed.

R1 = H, 1-5C alkyl, 3-6C cycloalkyl or a cationic salt moiety; A = CH<sub>2</sub>CH=CH (cis), CH=CHCH<sub>2</sub> (cis) or CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>; Z = CC, CH=CH (trans) or CH<sub>2</sub>CH<sub>2</sub>; One of R<sub>2</sub>, R<sub>3</sub> = H, and the other = F or OH (which may be modified), or R<sub>2</sub> and R<sub>3</sub> together = OCH<sub>2</sub>CH<sub>2</sub>O, or carbonyl; R<sub>4</sub> = (CH<sub>2</sub>)<sub>m</sub>Xphenyl or (CH<sub>2</sub>)<sub>p</sub>Z<sub>2</sub>. X = O or CH<sub>2</sub>; m = 1-6; phenyl is optionally substituted with halo, CH<sub>3</sub>, CF<sub>3</sub>, CN, OCH<sub>3</sub> or acetyl. p = 0-6; Z<sub>2</sub> = a defined optionally substituted bicyclic carbocycle or O-containing heterocycle.

The use of isopropyl [2R(1E,3R,3R)-7-[tetrahydro-2-(4-phenoxy-3-hydroxy-1-butenyl)-4-oxo-3-furanyl]heptanoate (Ia) (compound III) is specifically claimed.

23 pages

Drawings 0/0

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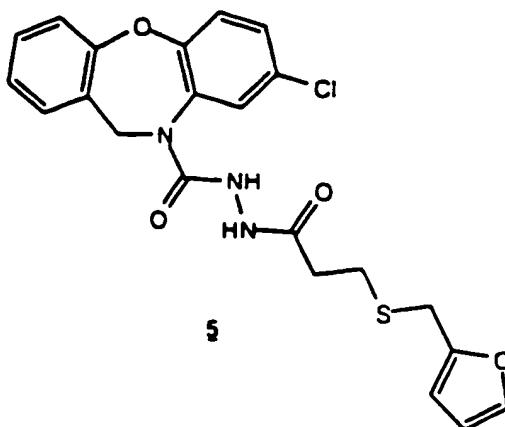
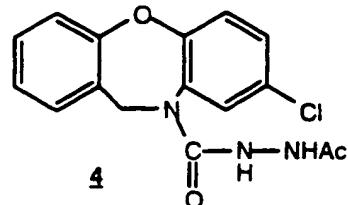
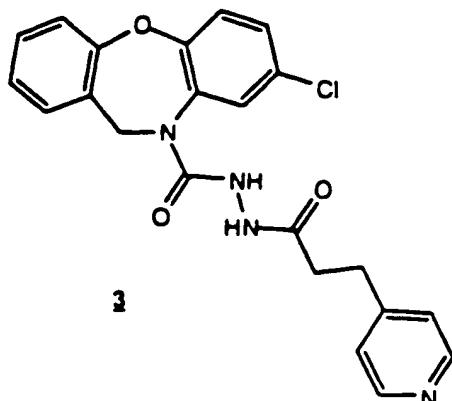
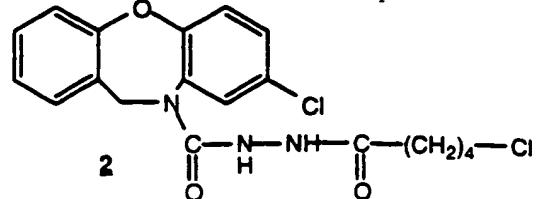
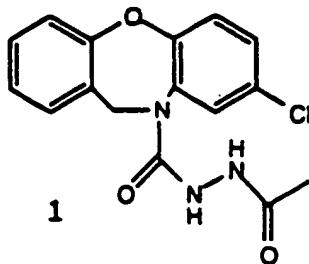
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PP - Cardiovascular

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*EP  
antagonists*



Recently, additional evidence for the involvement of PGE<sub>2</sub> and hence EP receptor subtypes in inflammation and pain has been reported. Specific monoclonal antibodies to PGE<sub>2</sub> (termed 2B5), that neutralize the activity of PGE<sub>2</sub>, were efficacious in a phenylbenzoquinone-induced model of nociception (20). Furthermore, these antibodies could reverse established hyperalgesia in a carrageenan-induced hyperalgesia model (21). The 2B5 antibodies were also able to substantially reverse edema

formation in a rat adjuvant-induced arthritis model (21). Remarkably, the efficacy of 2B5 in these inflammatory models was indistinguishable from that of indomethacin, a potent NSAID. In the most recent study, 2B5 was shown to be as efficacious as the COX-2 selective inhibitor, SC-58635, in a carrageenan-induced hyperalgesia model in rat (22). It is clear from these as well as previous studies that blockade of EP subtype receptor(s) could conceivably be as efficacious as NSAIDs in the treatment of inflammatory diseases without any of the undesirable side-effects associated with them.

**Gastric Antisecretory and Cytoprotective Agents** - PGs, especially PGE<sub>2</sub>, are known to have mucosal protective effects and act through a number of different mechanisms

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